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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,266	07/24/2001	James E. Fleming	390054.402	4134

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,266	FLEMING ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2004 and 20 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *34-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/3/04 has been entered.

Amendment Entry

2. Applicant's amendment and response, filed 5/20/04 is acknowledged and has been entered. Claims 9-24, 27, and 28 have been cancelled. Claims 34-40 have been added. Accordingly, claims 34-40 are pending and are under examination.

Rejections Moot

Claim Rejections - 35 USC § 112/102/103

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 9-24, 27, and 28 are now moot in light of Applicant's cancellation of the claims.

Trademark Usage

4. The use of the trademark "Oregon Green™" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 34, line 3, "ezymatically" should be --enzymatically--.

Claim 34 is vague and indefinite in reciting, "detecting a total amount of enzymatically altered molecule or dye, and correlating said total amount with a standard value, thereby quantitating viable cells in said sample" because as recited, it is unclear how the total amount of enzymatically altered molecule or dye should correlate with the recited "standard value" in order to provide an actual quantitation of the viable cells in the sample. It is further unclear what is encompassed by the recitation of a "standard value" as recited in the claim, i.e. positive control value? Please clarify.

Regarding claim 34, the phrase "standard value" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "standard value"), thereby rendering the scope of the claim unascertainable. Additionally, the term "standard value" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 38 is indefinite in reciting, "Oregon Green™". Trademark's compounds in claims need to be identified by their generic terminology.

In claim 39, "flurorometer" should be "fluorometer".

In claim 40, "detactably" should be --detectably--.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 34-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Breeuwer et al. (Applied and Environmental Microbiology 60(5): 1467-1472 (May 1994).

Breeuwer et al. teach a method for detecting cell viability using flow cytometry. Breeuwer et al. specifically teach contacting (vital staining) a sample containing yeast cells or bacterial cells with (carboxy)fluorescein diacetate which is a dye that diffuses into or penetrates (translocates) or is transported into the cells. In the cell, the

fluorescein diacetate dye is detectably altered by enzyme esterase activity (hydrolysis by nonspecific esterases) that takes place inside the viable cells in the sample. Fluorescein diacetate is retained by viable cells with intact membrane and lost by cells with damaged membrane. Breeuwer et al. teach detecting and quantifying (total amount of) fluorescence intensity of enzymatically-altered fluorescein diacetate in viable cells using flow cytometry (see Abstract). Breeuwer et al. provides that flow cytometer is calibrated using a calibration standard, i.e. comprising coumarin-6-labeled polystyrene latex particles (see page 1468, column 1). According to Breeuwer et al., dye (methylene blue) exclusion test and plate count methods are other tests for detecting or assessing viability (see page 1467, column 1).

7. Claim 34, 36, 37, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Sarkadi et al. (US 6,277,655).

Sarkadi et al. disclose a method and kit for quantifying viable cells. Sarkadi et al. disclose contacting the animal or yeast (fungal) cells with non-fluorescent form of calcein AM dye that diffuses into cell (membrane permeant dye). Inside viable cells, calcein AM is detectably altered into a fluorescent form, i.e. free calcein, by intracellular esterase enzymes (see column 10, lines 53-67 and column 6, lines 4-43). The fluorescent calcein accumulated in the cells is determined by fluorescent measurement using a fluorometer (see column 9, lines 12-24). Sarkadi et al. teaches use of control cell lines as standard for quantifying cells (see Example 1). Sarkadi et al. teach a kit for

use in the method which includes calcein AM dye and instructions for carrying out the method for detecting viability of the cells (see column 11, lines 20-30).

Response to Arguments

8. Applicant's arguments filed 5/20/04 have been fully considered but they are not persuasive.

A) Applicant argues that Breeuwer et al. fails to anticipate the presently claimed invention since it fails to describe a method of quantitating viable cells that involve correlating a measurement of enzymatic activity of a cell population with a standard value in order to quantitate viable cells in a sample.

In response, claim 34 only provides correlating the total amount [of enzymatically altered molecule or dye] with (undefined) standard value. Breeuwer et al. provides calibrating fluorescent intensity measurements in the flow cytometer using a calibration standard, i.e. standard value. Accordingly, it is proper for purposes of the anticipation rejection to interpret "standard value" to encompass general use of a control, a standard, or a calibrator having a “known” value because unpatented claims are given the broadest interpretation consistent with the specification.

B) Applicant argues that in Breeuwer et al. (Figure 9), the viable cells extrude the enzymatically altered fluorescent molecule, carboxyfluorescein, and that viable cells therefore, do not produce measurable fluorescence.

In response, Breeuwer et al. anticipates the claimed invention in teaching a method for detecting cell viability using flow cytometry by first contacting a yeast or bacterial cell sample with (carboxy)fluorescein diacetate which is a dye capable of diffusing or penetrating into the cells where it is detectably altered by enzyme esterase activity inside viable cells in the sample. Breeuwer et al. specifically teach that fluorescein diacetate is retained by viable cells with intact membrane and lost by cells with damaged membrane; hence, total amount of fluorescence intensity of enzymatically-altered fluorescein diacetate in viable cells is quantified using flow cytometry. Accordingly, Breeuwer et al. anticipates the claimed invention as recited in claim 34.

In as far as the extrusion of carboxyfluorescein by the viable cells, this study of kinetic activity of carboxyfluorescein to efflux from viable cells is caused to be stimulated by the addition of glucose into the cellular sample, and is not taught to be an inherent activity by carboxyfluorescein. Such teaching is intended to encompass a further embodiment of the teaching of Breeuwer et al. to detect cell viability using flow cytometry.

C) Applicant argues that Sarkadi et al. fails to anticipate the presently claimed invention, since it fails to teach the step of correlating a measurement of total enzymatic activity of a cell population with a standard value in order to quantitate viable cells in a sample.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the feature upon which applicant relies (i.e., correlating a measurement of total enzymatic activity of a cell population with a standard value) is not recited in the rejected claim. Alternatively, claim 34 only provides correlating the total amount [of enzymatically altered molecule or dye] with (undefined) standard value. Sarkadi et al. teaches use of control cell lines as standard for quantifying cells, i.e. standard value. Accordingly, it is proper for purposes of the anticipation rejection to interpret "standard value" to encompass general use of a control, a standard, or a calibrator having a "known" value or characteristic property because unpatented claims are given the broadest interpretation consistent with the specification.

D) Applicant argues that Sarkadi et al. teaches a method that requires determining the accumulation rate of fluorescence accumulation over time, and does not include correlating a total amount of enzymatically altered compound or dye to a standard value. Applicant argues that Sarkadi et al. do not teach and is not directed to a method of quantitating viable cells; but is rather directed to a method of examining the effect of inhibitors of transport proteins on the accumulation rate of a fluorescent compound in a cell, in order to identify modulators of multi-drug resistance.

Contrary to Applicant's argument, Sarkadi et al. disclose contacting the animal or yeast cells with non-fluorescent form of calcein AM dye, a membrane permeant dye, that diffuses into cell wherein it is detectably altered into a fluorescent form, i.e. free

calcein, by intracellular esterase enzymes, without the necessary presence or addition of active multi-drug resistance proteins. The total fluorescent calcein accumulated in the cells is determined by fluorescent measurement using a fluorometer (see specifically the teaching provided in columns 9-11). Accordingly, Sarkadi et al. reads on claim 34, as recited. The teaching of determination of accumulate rate of fluorescence over time and evaluation of active multi-drug resistance proteins encompasses a further embodiment of the teaching of Sarkadi et al.

In as far correlating to a standard value, claim 34 only provides correlating the total amount [of enzymatically altered molecule or dye] with (undefined) standard value. Sarkadi et al. teaches use of control cell lines as standard for quantifying cells, i.e. standard value. Accordingly, it is proper for purposes of the anticipation rejection to interpret "standard value" to encompass general use of a control, a standard, or a calibrator having a “known” value or characteristic property because unpatented claims are given the broadest interpretation consistent with the specification.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
July 29, 2004 GRG

Christopher L. Chin

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8/2/04